REMARKS

Claim 3 has been cancelled without prejudice. Claims 1, 2 and 4 - 22 are pending.

Claim 1 has been amended so that the ophthalmic pharmaceutical compositions are sustained release aqueous gels, dispersions or anhydrous salts for controlling and lowering intraocular pressure (IOP). Use of the term "basic active" has been eliminated. As now recited, the claimed compositions comprise a beta-blocker of the formula set forth in the claim and supported by the Specification at pages 1 - 2. The composition also includes an anionic mucomimetic polymer with a molecular weight of 50,000 to 6 million and which is further defined as having carboxylic acid functional groups, each of which has 2 to 7 carbon atoms. The mucomimetic polymer is present at a concentration such that the viscosity of the composition is from 1 to 20,000 cps. Support for the claim language can be found at pages 3 - 4 of the Specification. Finally, the composition of claim 1 includes a cation exchange resin present at a concentration of from about 0.05% to 10% by weight.

Claim 3 has been cancelled, and one of the limitations recited therein (aqueous dispersion) is now set forth in claim 1.

Claims 4, 5 and 6 have been revised to comport with the amendment to claim 1 and to depend from claim 1 rather than the now-cancelled claim 3.

Claim 7, which is directed to a method of controlling and lowering intraocular pressure, has been amended in a manner similar to claim 1.

Claims 10, 11 and 12 have been amended to reflect the changes in claim 7.

Claims 13 - 15 have been added and depend from claim 7. Claim 13 sets forth a concentration range for the beta-blocker, 14 claims a specific anionic mucomimetic polymer (carbomer) and 15 claims a specific cation exchange resin sodium poly(styrene-divinylbenzene) sulfonic acid.

Claim 16, depending from claim 7, has been added and claims specific concentrations for the beta-blocker, the polymer and the resin.

Composition claims 17 - 19 have been added and depend from claim 1. They claim the same specific concentration range and polymer and resin respectively as set forth in the method claims 13 - 15.

Claim 20 has been added and depends from claim 1. It claims a specific beta-blocker, polymer and resin at specific concentrations.

The new independent claims (21 and 22) have been added which set forth a composition and method respectively comprising IOP lowering drugs within the meaning of "basic active", and disclosed in the specification, but not covered by claims 1 and 7.

Claims 1 - 12 have been rejected under 35 USC 112, first paragraph, the Examiner stating that the disclosure is enabling only for claims limited in accordance with pages 2 - 9 of the Specification. Specifically the Examiner has objected to the language "a basic active", "an anionic mucomimetic polymer", "a cation exchange resin" and "the basic active is...isoxaprolol".

Each of the Examiner's specific objections have been addressed by the above-discussed claim amendments. The term "basic active" has not been used, rather, the term "beta blocker" in conjunction with a defined structure has been recited. In addition, new claims 21 and 22 set forth disclosed drugs, known to treat ocular hypertension, which were included in the originally filed claims as

"basic actives". As set forth in the amended claims "anionic mucomimetic polymer" and "cation exchange resin" have been further defined in terms disclosed in the Specification. With regards to the Examiner's rejection directed to the language in claims 6 and 12, "the basic active... ...isoxaprolol", Applicants respectfully point out that all of the cited drugs are known compounds and were disclosed in the original Specification, which included claims 6 and 12. Therefore, the disclosure is enabling as required by 35 USC 112, first paragraph.

The Examiner has rejected claims 1 - 12 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner states that claims 1 - 6 are indefinite for failing to set forth proportions and that claims 7 - 12 are indefinite for failing to set out the amount of active ingredient or composition containing the same to be administered in the claimed method. Furthermore, the Examiner has objected to the term "controlling" as indefinite as to just what type of effect is desired or expected. In addition, claims 1, 3 and 7 are rejected as indefinite due to the terms "a basic active", "an anionic ... polymer" and "a cation resin". Applicants respectfully submit that the amendments to the claims presented herein overcome the Examiner's rejection based on 35 USC 112, second paragraph.

The amount of beta-blocker has been defined functionally in that a therapeutically effective amount is required. This functional language has a clear and definite meaning to a person skilled in the art. In addition, the amount of anionic mucomimetic polymer is also defined functionally in that an amount necessary to produce a viscosity of about 1 to about 20,000 cps. is claimed. Furthermore, a specific range for cation exchange resin (0.05 - 10.0%) has now been set forth in the claims. The present amendments serve to define two of the components functionally and one with a specific range. Applicants have amended the claims to overcome the Examiner's

rejection of "controlling" as indefinite by inserting language to state that the beta-blocker also lowers intraocular pressure.

Additional claims 13 - 20 define particular proportions for the ingredients.

Claims 1 - 12 have been rejected under 35 USC 103 as unpatentable over Michaels, U.S. Patent No. 3,867,519, Schoenwald et al., U.S. Patent No. 4,271,143 and Schoenwald et al., U.S. Patent No. 4,407,792 in view of Rankin, U.S. Patent No. 3,987,163, Mamajek et al., U.S. Patent No. 4,207,890, Samejima et al., U.S. Patent No. 4,462,982 and Heath et al., Chem. Abstracts, Vol.98, 210936j (1983). Applicants respectfully traverse the rejection and request reconsideration.

Applicants submit that for the above-cited combination of references to be effective under 35 USC 103, the references themselves must suggest the combination. The references cited do not suggest the combination of cation exchange resins and mucomimetic polymers for the purposes of both sustained topical ophthalmic drug release and improved comfort to the eye.

The Michaels and Schoenwald et al. patents disclose ophthalmic drugs in combination with high molecular weight polymers, however, there is no suggestion for the incorporation of a cation exchange resin, nor the benefits to be obtained from the use of a cationic exchange resin. Rankin discloses an ophthalmic solution which contains a polystyrene sulfonate polymer, however there is no suggestion for the incorporation of a cation exchange resin in the composition of this invention. Nor is there a suggestion in Rankin for the incorporation of the polystyrene sulfonate polymers into the anionic polymer-containing compositions of Michaels or Schoenwald. Therefore, a combination of these references must be based on the use of impermissible hindsight reasoning. Moreover, even if the references could be properly combined, when the invention is

considered as a whole under 35 USC 103, the references are insufficient to negate patentability.

Applicants point out that there is no suggestion for the use of the polymer envelope of Mamajek et al. or the microcapsules of Samejima et al. in conjunction with topical ophthalmic compositions. Mamajek et al. fail to disclose compositions similar to Applicants' ophthalmic compositions (gel, pourable liquid or anhydrous salt) and fail to set forth any teaching for administration of sustained release topical ophthalmic compositions. Therefore, the combination of Mamajek et al. with Michaels and/or Schoenwald et al. fails to teach the claimed invention within 35 USC 103. Samejima et al. disclose ethylcellulose microcapsules wherein a polymer material is incorporated into the walls and/or the core material. The capsules are designed for rapid release of the core material into digestive organs such as the stomach. Ophthalmic compositions are not contemplated and therefore Samejima et al. suffers the same deficiencies as Mamajek et al.

Applicants also points out that Heath et al. involves an in vitro study in which Amberlite, a cation exchange resin, is used to adsorb drugs from blood. There is no relation of Heath et al. to the present invention in that sustained release ophthalmic compositions are not disclosed. Furthermore, combination of this reference with the basic patents relied on by the Examiner would not suggest Applicants' invention within the meaning of 35 USC 103, since there is no teaching among these references that a cation exchange resin could be utilized in combination with an anionic mucomimetic polymer to provide improved topical ophthalmic delivery of beta blockers.

Furthermore, it is unexpected that Applicants' claimed combination of cation exchange resin, mucomimetic polymer and an IOP lowering drug would result in an improved composition and method for controlling and lowering intraocular pressure in that the compositions provide for both sustained release and comfort to the eye. In order

to further illustrate the unexpected results achieved with Applicants' invention, Applicants will submit a Declaration under 37 CFR 1.132 of Larry A. Bruce, Ph.D. In this Declaration a number of examples are set forth and explained with regard to the sustained release properties of the claimed compositions and their increased comfort relative to compositions without the resins and polymers used in this invention.

In the forthcoming Declaration and accompanying data, it is shown that a composition encompassed by the claims of this invention exhibits sustained release properties due to the incorporation of both a cation exchange resin (Amberlite) and an anionic mucomimetic polymer (Carbomer 934P). Moreover, in support of Applicants' claim of unexpected results, the data also illustrate that this composition provides for a dramatic decrease in the amount of discomfort, in particular stinging and associated effects of this discomfort, experienced by patients, compared to the administration of the drug (betaxolol) without the polymer or cation exchange resin.

First, with regards to sustained release, the results of two studies will be presented. One compares the ocular bioavailability (the amount of drug present in the aqueous humor of rabbits at periodic times) of a 0.25% betaxolol, 0.25% Amberlite and 0.20% Carbopol 934P composition encompassed by the claims of the present invention with a 0.50 betaxolol aqueous solution known as 0.5% BETOPTIC (see attached copies of PDR pages for this composition). In summary, it was shown that after 10 minutes, 1.4 ug/ml was found in the aqueous humor of the eyes of both those rabbits dosed with the 0.25% suspension and the 0.5% aqueous solution. Peak concentrations of 1.7 ug/ml for both compositions were observed 20 minutes from dosing. The mean concentration versus time profiles for the two treatments were so closely matched that an analysis of variance for the drug concentration at each sampling through 90 minutes showed no significant difference. The results of this study indicate that the 0.25% suspension provides aqueous humor concentrations equivalent to

the 0.5% aqueous solution due to the sustained release characteristics provided by the Amberlite and Carbopol present in the suspension. This conclusion is also supported by a clinical study in which the IOP of human glaucoma patients dosed with the 0.25% suspension and those with the 0.5% aqueous solution were compared. The average IOP values for both groups at 1, 2 and 4 weeks were significantly reduced, and the average IOP values for each group were not statistically different from each other at the respective measurement times.

Secondly, with regards to finding that compositions of the claimed invention provide for decreased discomfort, data has been collected regarding the discomfort associated with the currently marketed 0.5% aqueous solution and the 0.25% suspension according to the invention. In the product information provided in the attached PDR pages, it can be seen that 1 in 4 patients (25%) experienced discomfort on administration of 0.5% BETOPTIC. In contrast, and unexpectedly, only 7.9% of patients with primary open angle glaucoma (ongoing study) reported discomfort on use of the 0.25% suspension encompassed by the claims of the present invention (a decrease of about 68%). Furthermore, in another study, only 1 of 94 patients who have completed six months of a long-term study regarding the efficacy and safety of the 0.25% betaxolol suspension have reported discomfort.

The references cited against the claimed invention do not disclose or suggest that either the polymer or the ion exchange resin or the two together can be used to decrease discomfort (stinging) associated with the instillation of IOP lowering drugs, in particular betaxolol. The dramatic stinging of many IOP lowering drugs like betaxolol and the associated effects of such discomfort, such as poor patient compliance, are overcome by the compositions of the claimed invention (see the Specification at p. 3). Thus, the invention represents a solution to very significant problems associated with prior art glaucoma therapies.

Applicants' respectfully request reconsideration of the

Examiner's rejection under 35 USC 103. The data discussed herein, which supports Applicants' assertion of unexpected results, will be more fully presented in a Rule 132 Affidavit which will be submitted very shortly, prior to the Examiner's consideration of this Amendment.

The Examiner has indicated that Applicants "appear to allege critically as to the presen[ce] of lecithin." Respectfully, Applicants cannot respond to this point as they fail to understand the allegation. No allegation as to the criticality of lecithin has been made.

Wherefore: Applicants' claims are in condition for allowance and notice of such allowance is respectfully requested.

Respectfully submitted,
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